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B01F 3/12

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FR 002695135 A US 4907893 A
US 4523855 A

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(54) Abstract Title
Rotatable mixer for sample recovery

(57) Cascade impactors are used for testing the size distribution of particles emitted by pharmaceutical inhalers. The inlet used to introduce the particles into the cascade impactors are called USP (United States Pharmacopeia) induction ports. Particulate matter needs to be removed from the inside of these ports after each test by means of a solvent which dissolves the active drug material. The solvent is mixed with the particulates in mixer 12 which supports cradle 24 on which USP induction port 50 is attached by means of screws 32A, 32B and cup members 36A, 36B. The cup members 36A, 36B serve to cover the open ends 42A and 44A of the induction port 50. The cradle is then rotatably driven by means of motor 46 which drives shaft 22A and the motor may be controlled by computer 48. Pre-separators (Fig 4, 60) , which are used for removing large diluent particles prior to the induction port, may also be mixed and cleaned in a similar manner.

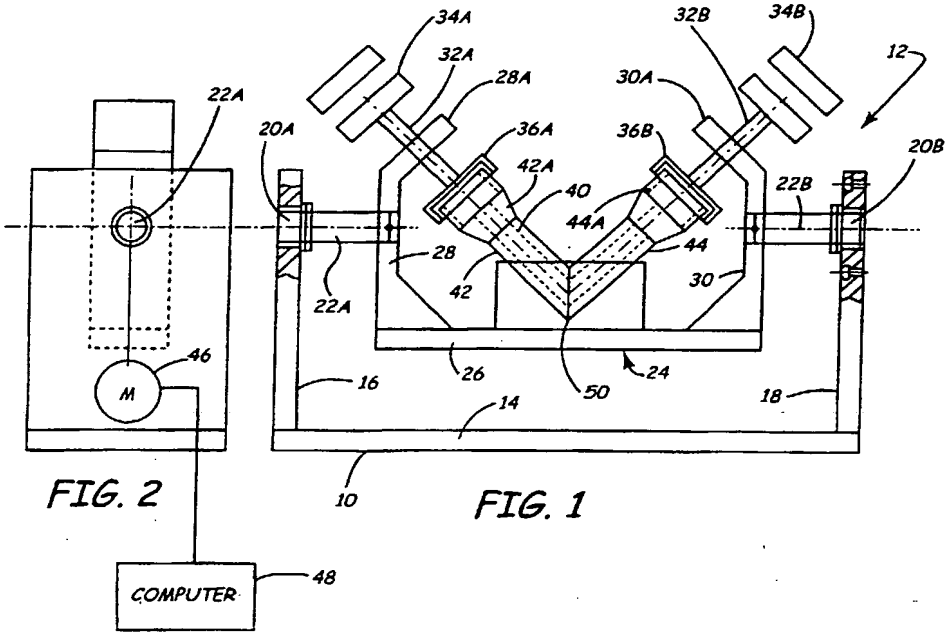

FIG. 2

FIG. 1

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At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

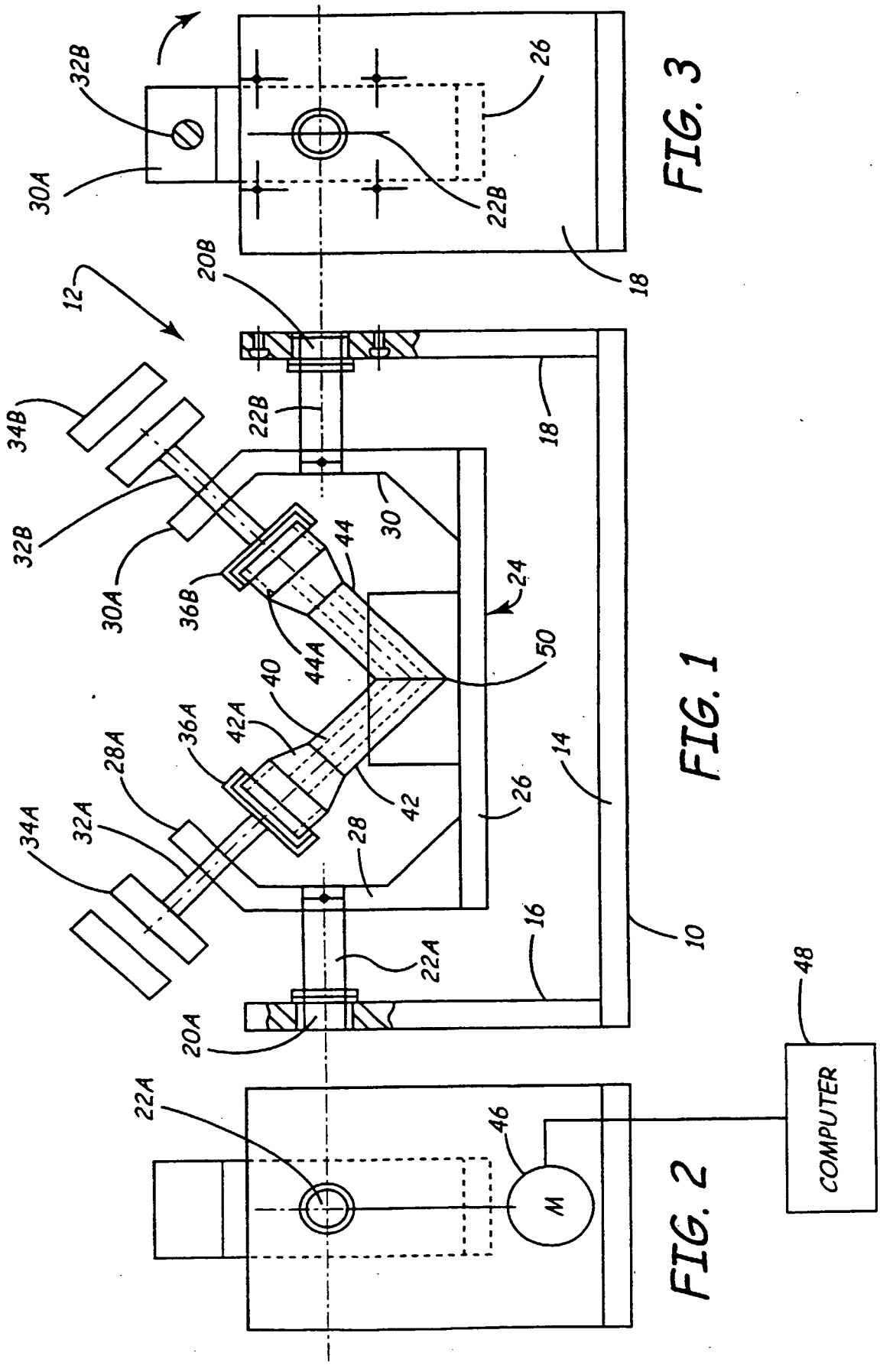

FIG. 3

FIG. 1

FIG. 2

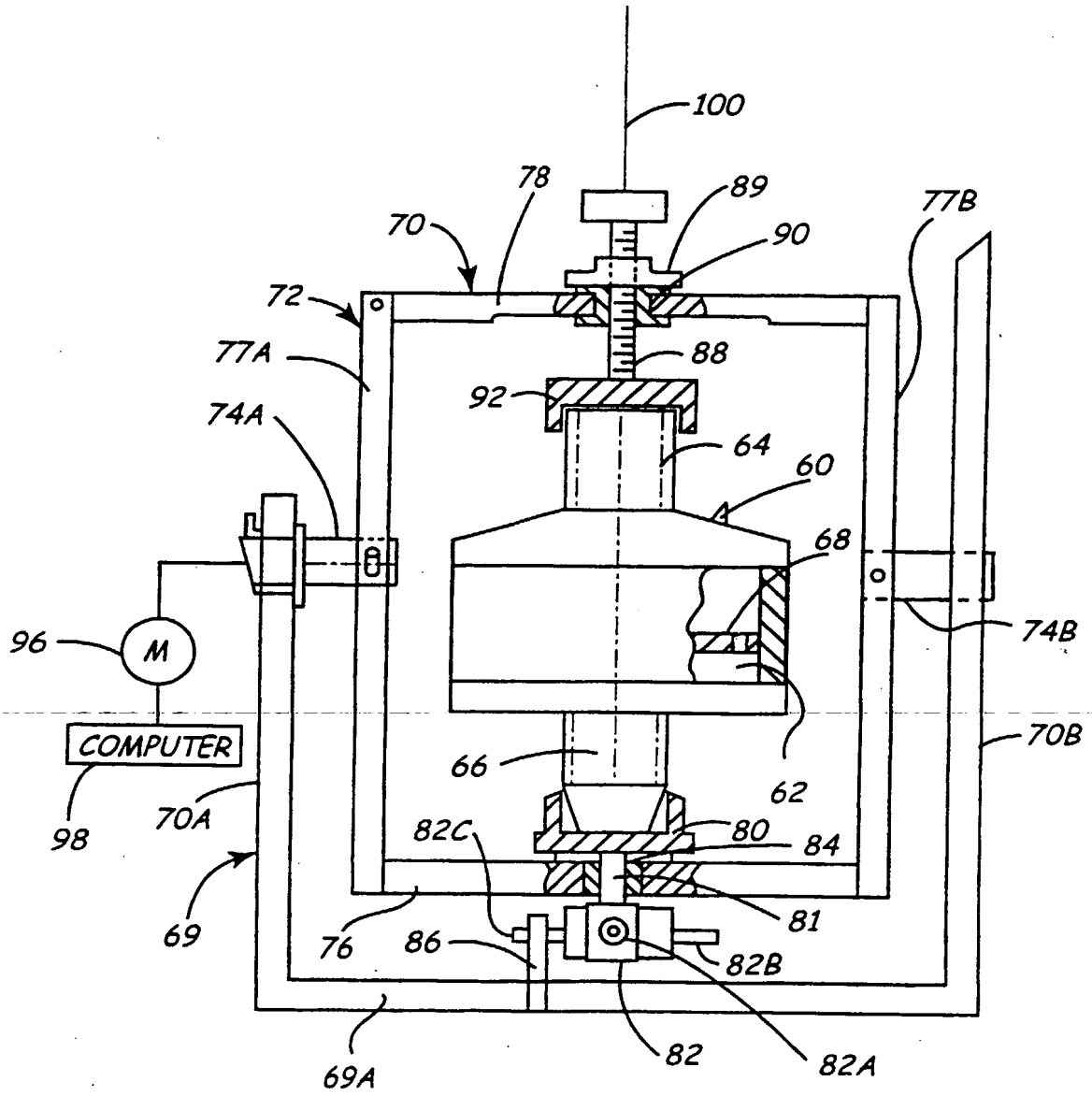
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FIG. 4

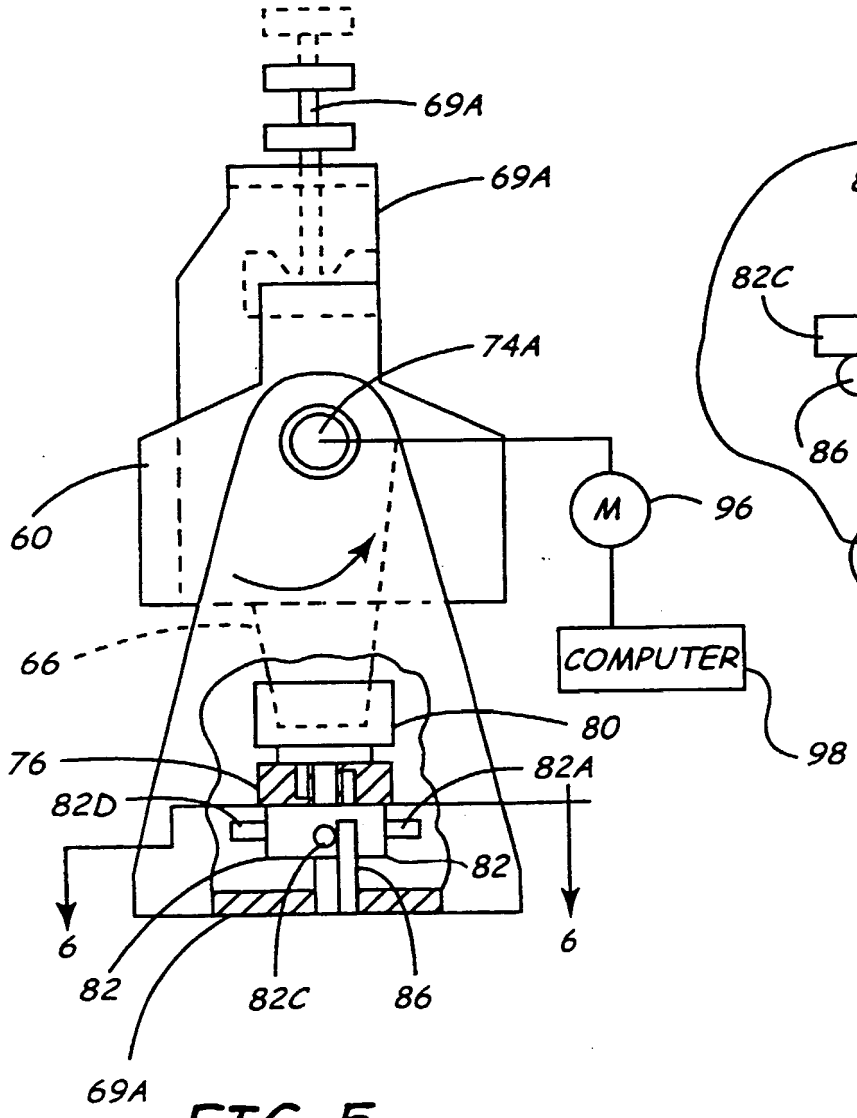

FIG. 5

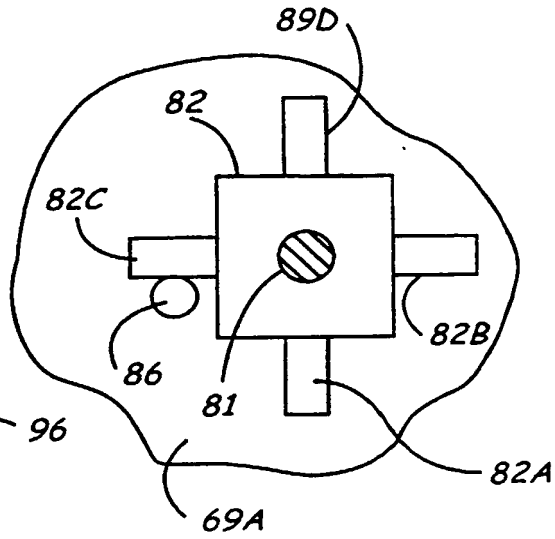

FIG. 6

MIXING DEVICES FOR SAMPLE RECOVERY FROM A USP INDUCTION PORT OR A PRE-SEPARATOR

BACKGROUND OF THE INVENTION

Two mixers are disclosed which are used for agitating solvents in components of dry powder inhalers to recover particles of internal clinging to wall of such components. The mixers are designed to assist laboratory personnel in the measurement of the size distribution of particulate matter emitted from metered-dose, dry-powder, and similar inhalers. Such inhalers are in common use for the treatment of asthma today and are increasingly important in the therapeutic delivery of pharmaceutical products of biotechnology.

Inhalers must be tested regularly both during laboratory development of new products and for quality control and assurance for commercially sold products. The testing includes the measurement of the size distribution of particles emitted by the inhalers. The United States Pharmacopeia (USP) and similar British, European, and Japanese regulatory documents describe the use of cascade impaction devices as the acceptable method for measuring size distribution. Further, these international compendia describe the inlet that must be used to introduce the particles into the cascade impactor. This inlet is known commonly as the USP Induction Port and is shown on page 1902 of USP 24, Section 601.

Because particulate matter accumulates in this induction port during each test of an inhaler device, the laboratory analyst doing the testing must quantify the mass of active drug material deposited in the induction port. Typically, this procedure involves washing the inside walls of the induction port with a solvent known to dissolve the active drug ingredient and in some manner insuring that all drug material is recovered from the inside walls of the induction port. The wash solvent is then analyzed, typically by high-performance liquid chromatography (HPLC), to quantify the drug material.

The procedure of removing the drug material from the walls of the induction port is typically an ad hoc one with no assurance that all material is recovered. Further, the complete washing of the walls can consume a minimum of 50 ml of solvent and up to 200 ml of solvent. Consequently, the active drug compound is diluted with solvent, and the analysis via HPLC is relatively insensitive to the presence of the drug material, compromising the accuracy of the overall test.

In addition, pre-separators are used in many impactors. Dry-powder inhalers typically contain large diluent particles along with the active drug material. These diluent particles would interfere with the functioning of the cascade impactor designed to recover the dry particles allowed to enter the impactor during a test. Consequently, when an analyst

tests a DPI, a pre-separator is attached to the inlet of the cascade impactor. Some drug material accumulates in this pre-separator during testing, and the active drug material captured in the pre-separator must be quantified. This procedure requires washing with a known amount of solvent, typically 50 ml to 200 ml in prior art procedures, and/or shaking the device.

SUMMARY OF THE INVENTION

The present invention relates to mixing devices that allow a user to add a minimum amount of solvent to parts that have recesses and bends, and to mix the solvent, while unattended, with the active drug material that has been clinging to the walls. This will thoroughly wash the walls, and cause the active drug material to be dissolved in the solvent. The handling of the solvent to recover the material of interest after this washing process is according to standards.

Mixing devices embodying the present invention include fixtures that will hold the induction port, on the one hand, and a pre-separator on the other, and will rotate these components with the solvent contained in the chambers or passageways, after capping or sealing the openings, so the solvent acts on the material clinging to the interior surfaces.

The mixing devices insure that all of the surface areas are contacted by the solvent during the mixing process, so that it is known that all of the

active drug material has been dissolved and is available for analysis.

The mixing devices are made so that they will permit use of a minimum amount of the solvent, and will yet provide adequate mixing to insure that all of the active drug materials are released.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a side elevational view of a mixing device utilized with a USP Induction Port;

Figure 2 is a first end elevational view thereof;

Figure 3 is a second end elevational view thereof;

Figure 4 is a side elevational view of a second mixing device adapted specifically for a pre-separator, for holding it in place for agitation;

Figure 5 is a side elevational view showing the mixing stand in position; and

Figure 6 is a schematic sectional view taken on line 6--6 in Figure 4.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring to Figure 1, a stand or frame 10 is used as a frame for the mixing device indicated generally at 12. The stand has a base 14, and a pair of upright end members 16 and 18. The upright end members support bearings 20A and 20B, that in turn rotatably mount shaft portions 22A and 22B that are used for supporting a cradle 24. The cradle 24 has a base 26, and end supports 28 and 30 fixed to the base

end supports, as shown, have bent wall portions 28A and 30A that are formed at a substantially 45° to the main portions of the end supports. These bent wall portions have threaded openings to support threaded rods 32A and 32B. The threaded rods have handles 34A and 34B for rotating them manually, and in addition, each of the rods 32A and 32B holds a cap or cup structure 36A and 36B which are on the inner sides of the bent wall portions 28A and 30A, and are positioned between the end supports 28 and 30.

A USP Induction Port is indicated at 40, and it has two tubular sections 42 and 44, at right angles to each other in a fixed assembly. The tubular sections 42 and 44 have standard open end connections or couplings shown at 42A and 44A. The tubular sections form a passageway through the interiors. In order to support the induction port 40 in the cradle 24, the screws 32A and 32B are backed out, so that the cup members 36A and 36B will permit the USP Inlet Port to slip into place, and then the screws are threaded down so that the cup members 36A and 36B cover the open ends of the couplings 42A and 44A. Prior to putting the inlet in position, and closing it off, a suitable amount of solvent is added to the interior chamber.

The cradle is then rotatably driven, by driving it with a motor 46 that can be operated through a computer control 48 as to the timing, speed, and the amount of rotation. Pneumatic motors

could be used, but a stepper motor is shown as an exemplary embodiment.

The USP inlet will rotate around, and the solvent that is retained inside the tube will flow back and forth as the unit is rotated, and will contact all of the interior surfaces of the tubular sections 42 and 44.

In operation, the USP Inlet 40 is charged with a minimum amount of solvent, generally approximately 10 ml to 20 ml, and then the unit is put into place and the screws 32A and 32B are threaded so the caps 36A and 36B hold the inlet between the caps and seal the end openings.

The entire inlet and cradle assembly then is rotated, and the solvent will slosh or flow back and forth between both ends and the center portion 50 of the inlet, to insure adequate passage of the solvent over the surfaces to dissolve the particles of the active drug material.

Because the rotation is done by machine, the user not only saves time, because he can be at other tasks during the time that it is being used, but he avoids the tedium of having to shake the inlet port himself and to look into it to see if all the drug material has been recovered. Typically, the device can be rotated continuously or in one direction, or can be moved back and forth about the axis of the shafts 22A and 22B.

A second mixer is shown in Figures 4 through 6, and in this instance, a pre-separator assembly 60 is being cleaned. It has an interior chamber, shown fragmentarily at 62, an inlet 64, and an outlet tube 66. In some of these pre-separators, there is an impaction plate in the center portions that is shown schematically at 68, but in any event the use is with the flow of an aerosol through the inlet 64, and the interior chamber 62 to the outlet 66.

The fixture of the present invention includes a frame 69 that has a base 69A supporting upright members 70A and 70B, that in turn rotatably mount a cradle 72. The cradle 72 has shafts 74A and 74B that are rotatably mounted on suitable bearings on the upright members 70A and 70B of the frame 69.

The cradle 72 has a lower support cross member 76, and an upper cross member 78 joining side members 77A and 77B. These cross members support hold cups for holding the pre-separator 60. The lower cross member 76 has an upwardly facing cup 80 that will receive the end of the outlet 66, as shown. This cup 80 is supported on the cross member 76 and has a shaft 81 that rotates in a bearing in the cross member 76. A turnstile drive member 82 is driven by the lower end of shaft 81 that has four arms that protrude at 90° to each other. Two of the arms 82A and 82B are shown in Figure 4, and two of the arms 82C and 82D are shown in Figure 5. The cup 80 is

rotatably mounted in the bearing 84 so that the cup will freely rotate.

An upright post 86 is fixed to the lower frame member 68A and extends upwardly. This post 68 acts as a turnstile, as will be explained.

The upper cross member 78 rotatably supports a screw threaded shaft 88 that threads through a nut 89 that is mounted in a bearing 90 so the screw threaded shaft can rotate and also can be threadably adjusted. In other words, the bearing hub will permit the nut and shaft to rotate, but the screw threaded shaft 88 can be threaded, to move the cap shown at 92 vertically toward and away from the pre-separator housing 60.

In use, the device can be driven with a suitable motor 96 that is driven from a computer 98 in a normal manner. This too can be a stepper motor or could be a pneumatic rotary actuator as desired. It also could be a reversible DC motor.

The screw threaded shaft 88 has a manual handle 88A, can be threaded toward and away from the cross member 78.

When the pre-separator 60 is to be cleaned with a solvent, it is placed with the outlet 66 in the lower cup 80, and then solvent is put into the inlet 64, again using a limited amount of the solvent, probably in the range of 30-40 ml. Then the cup 92 is lowered into position to hold the pre-separator in a sealed position. Suitable gasketing

materials can be used in the cups in this form of the invention, as well as the other form of the invention, to insure no leakage.

Once the pre-separator 60 is held between the cups 80 and 92, the motor 96 can be started and the unit can be rotated 360° about the shafts 74A and 74B. As it rotates, the post 84 will engage one of the arms 82A-82D and will rotate the pre-separator 60 about the upright axis, that is indicated at 100.

In this way, the pre-separator is indexed 90° about the upright axis for each revolution about the horizontal axis. If desired the pre-separator can be rotated a selected number of degrees and then rotated in a reverse direction for proper use of the solvent in dissolving the drug particles of interest.

The rotation about the vertical axis caused by the turnstile type post and cross member, insures that there are no dead zones inside the pre-separator that remain unwashed or untouched by the solvent. The user can also reverse the direction of the rotation about the horizontal axis to effect complete mixing.

The mixing devices shown improve the repeatability and uniformity of the sample recovery process from the pre-separator and from the USP Induction Port.

Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that

changes may be made in form and detail without departing from the spirit and scope of the invention.

CLAIMS:

1. A mixer device for an inlet component for a particle impactor, wherein particles may cling to surfaces of an interior component of the component, comprising a rotatable cradle supporting the component, and a drive to rotate the cradle a desired amount about an axis.

2. The mixer device of claim 1, wherein the inlet component has at least one open end to receive a solvent, and the cradle has an adjustable cap to overlie and close the open end.

3. The mixer device of claim 1 or claim 2, wherein the inlet component has two open ends, and a pair of adjustable caps on the cradle to overlie and close the open ends, the caps comprising supports for supporting the inlet component on the cradle.

4. A mixer device substantially as hereinbefore described with reference to the accompanying drawings.

5. A cascade impactor including a mixer device as claimed in any preceding claim.

Application No: GB 0129158.2 **Examiner:** Conal Clynch
Claims searched: 1-5 **Date of search:** 3 April 2002

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.T):

Int Cl (Ed.7): B01F 3/12

Other: Online: EPODOC, JAPIO, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	FR 002695135 A	(Francois Valentin) see Figures 1-3 & WPI Abstract Acc No FR2695135 A 1994-120592 [15]	1
X	US 4907893 A	(Niemeck) see Figures 1-6 & column 3 lines 12-45	1
X	US 4523855 A	(Walker) see the Figures & column 4 lines 24-49	1

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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